General

Guideline Title

Endocrine therapy for hormone receptor–positive metastatic breast cancer: American Society of Clinical Oncology guideline.

Bibliographic Source(s)

Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, Fallowfield L, Fowble B, Ingle JN, Jahanzeb M, Johnston SRD, Korde LA, Khatcheressian JL, Mehta RS, Muss HB, Burstein HJ. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology guideline. J Clin Oncol. 2016 Sep 1;34(25):3069-103. [94 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the rating of evidence (High, Intermediate, Low, Insufficient); types of recommendations (Evidence based, Formal consensus, Informal consensus, No recommendation); and strength of recommendations (Strong, Moderate, Weak) are provided at the end of the "Major Recommendations" field.

Clinical Question 1

Is there an optimal (defined throughout this guideline as treatments with demonstrated benefits in both treatment-related and quality-of-life outcomes) first-line endocrine therapy regimen for hormone receptor (HR)-positive metastatic breast cancer (MBC)?

Question 1.1

For postmenopausal women: What are the optimal sequence and duration?

Recommendation 1.1

Postmenopausal women with HR-positive MBC should be offered aromatase inhibitors (AIs) as first-line endocrine therapy (see Figure 1 in the original guideline document) (Type: evidence based, benefits

outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Question 1.2

Should hormone therapy be administered in combination with other hormonal agents or chemotherapy?

Recommendation 1.2

Combination hormone therapy with fulvestrant, with a loading dose followed by 500 mg every 28 days, plus a nonsteroidal AI may be offered to patients with MBC without prior exposure to adjuvant endocrine therapy (see Figure 1 in the original guideline document) (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Question 1.3

For premenopausal women: What is the optimal timing of ovarian suppression or ablation? Should all patients have their ovaries suppressed? What is the best partner hormonal agent in this setting?

Recommendation 1.3

Premenopausal women with HR-positive MBC should be offered ovarian suppression or ablation in combination with hormone therapy. Ovarian suppression with either gonadotropin-releasing hormone (GnRH) agonists or ablation with oophorectomy seems to achieve similar results in MBC. For most patients, clinicians should use guidelines for postmenopausal women to guide the choice of hormone treatment, although sequential therapy can also be considered. Patients without exposure to prior hormone therapy can also be treated with tamoxifen or ovarian suppression or ablation alone, although combination therapy is preferred (see Figure 2 in the original guideline document). Treatment should be on the basis of the biology of the tumor and the menopausal status of the patient, with careful attention paid to production of ovarian estrogen (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Question 1.4

Are there demonstrated differences between pre- and postmenopausal patients?

Recommendation 1.4

Treatment should take into account the biology of the tumor and the menopausal status of the patient, with careful attention paid to ovarian production of estrogen (see Figure 2 in the original guideline document) (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Clinical Question 2

Is there an optimal second-line or later endocrine therapy for HR-positive MBC?

Question 2.1

Should other treatment or disease-free interval play a role in treatment selection?

Recommendation 2.1

The choice of second-line hormone therapy should take into account prior treatment exposure and response to previous endocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Question 2.2

Which hormone therapy should be offered?

Recommendation 2.2

Sequential hormone therapy should be offered to patients with endocrine-responsive disease. Options are

shown in Figure 1 in the original guideline document (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Question 2.3

What are the optimal timing, dose, schedule, and duration of treatment?

Recommendation 2.3

Fulvestrant should be administered using the 500-mg dose and with a loading schedule (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Clinical Question 3

How or should endocrine therapies be used in combination or sequence with mammalian target of rapamycin (mTOR) inhibitors (everolimus) or cyclin-dependent kinase (CDK) 4/6 inhibitors (palbociclib)?

Question 3.1

How or should endocrine therapies be used in combination or sequence with mTOR inhibitors?

Recommendation 3.1

Exemestane and everolimus may be offered to postmenopausal women with HR-positive MBC who experience progression during treatment with nonsteroidal AIs, either before or after treatment with fulvestrant, because progression-free survival (PFS) but not overall survival (OS) was improved compared with exemestane alone. Other options are shown in Figures 1 and 2 in the original guideline document. This combination should not be offered as first-line therapy for patients who experience relapse >12 months from prior nonsteroidal AI therapy or for those who are naïve to hormone therapy (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Question 3.2

How or should endocrine therapies be used in combination or sequence with CDK 4/6 inhibitors?

Recommendation 3.2

A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment-naïve HR-positive MBC; PFS but not OS was improved compared with the nonsteroidal AI letrozole alone. Other options are shown in Figures 1 and 2 in the original guideline document. The accelerated approval of palbociclib is dependent on results of an ongoing phase III trial in the same setting (see online Data Supplement 8; PALOMA-2 trial [see the "Availability of Companion Documents" field]). Results from the PALOMA-2 trial will be presented at the ASCO 2016 Annual Meeting. A press release confirms that the trial met its primary end point. Letrozole plus palbociclib improved PFS compared with letrozole alone as first-line therapy for HR-positive metastatic breast cancer in postmenopausal women. Survival data are not yet available.

Palbociclib may also be offered in combination with fulvestrant in patients exposed to prior hormone therapy and up to one line of chemotherapy, on the basis of data from the phase III PALOMA-3 trial. PFS was improved compared with fulvestrant alone; OS data are immature (Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: intermediate).

Clinical Question 4

Does estrogen or progesterone expression (high versus low expression) affect hormone therapy considerations and modify recommendations for hormone therapy—either the recommended agents or dosing details—among pre-, peri-, and postmenopausal women?

Recommendation 4

Hormone therapy should be offered to patients whose tumors express any level of estrogen receptor (ER)

and/or progesterone receptor (PR) (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Clinical Question 5

How does adjuvant treatment affect recommendations for treatment in the metastatic or advanced setting?

Recommendation 5

Treatment recommendations should be offered on the basis of type of adjuvant treatment, disease-free interval, and extent of disease at the time of recurrence (see Figures 1 and 2 in the original guideline document). A specific hormonal agent may be used again if recurrence occurs >12 months from last treatment (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Clinical Question 6

In which patients or settings is hormone therapy recommended over chemotherapy?

Recommendation 6

Endocrine therapy should be recommended as initial treatment for patients with HR-positive MBC, except for patients with immediately life-threatening disease or for those who experience rapid visceral recurrence during adjuvant endocrine therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Question 6.1

Is there a role for combined cytotoxic and endocrine therapies?

Recommendation 6.1

The use of combined endocrine therapy and chemotherapy is not recommended (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Question 6.2

What is the optimal duration of treatment with hormone therapy?

Recommendation 6.2

Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms. Tumor markers or circulating tumor cells should not be used as the sole criteria for determining progression (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Clinical Question 7

Is there a role for additional biomarkers in the selection of treatment for patients for HR-positive disease?

Recommendation 7

Use of additional biomarkers is experimental and should be reserved for selection of treatment in clinical trials. There is no routine clinical role for genomic or expression profiling in the selection of treatment for HR-positive MBC (Type: consensus based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Question 7.1

What is the role of genomic profiling or intrinsic subtypes in this population?

Recommendation 7.1

Genomic or expression profiling should not be used to select treatment for HR-positive MBC (Type: consensus based, benefits outweigh harms; Evidence quality: low; Strength of recommendation: moderate).

Clinical Question 8

How does human epidermal growth factor receptor 2 (HER2) positivity affect treatment of patients with HR-positive MBC?

Recommendation 8

The addition of HER2-targeted therapy to first-line AIs should be offered to patients with HR-positive, HER2-positive MBC in whom chemotherapy is not immediately indicated. The addition of HER2-targeted therapy to first-line AIs improved PFS, without a demonstrated improvement in OS. HER2-targeted therapy combined with chemotherapy resulted in improvements in OS and is the preferred first-line approach in most cases (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Clinical Question 9

What are the future directions for treatment in this patient population?

Recommendation 9

Patients should be encouraged to consider enrolling in clinical trials, including those receiving treatment in the first-line setting. Multiple clinical trials are ongoing or planned, with a focus on improving response to hormone therapy in metastatic disease (Type: evidence and consensus based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Definitions

Guide for Rating Strength of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus

Type of Recommendation	Definition
	process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement (see the "Availability of Companion Documents" field).
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment
Hormone therapy for premenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment

Scope

Disease/Condition(s)

Hormone receptor (HR)–positive metastatic breast cancer (MBC)

Guideline Category

Treatment

Clinical Specialty

Obstetrics and Gynecology

Oncology

Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Patients

Physician Assistants

Physicians

Social Workers

Guideline Objective(s)

To develop recommendations about endocrine therapy for women with hormone receptor (HR)–positive metastatic breast cancer (MBC)

Target Population

Women with hormone receptor (HR)–positive metastatic breast cancer (MBC)

Interventions and Practices Considered

1. General considerations for offering endocrine therapy (timing, sequence, duration, menopausal status, etc.)
2. First-line endocrine therapy
    - Aromatase inhibitors (AIs)
    - Combination hormone therapy with a nonsteroidal AI and fulvestrant 500 mg, with a loading schedule
    - Ovarian suppression or ablation plus hormone therapy for premenopausal women
3. Second-line or later therapy
    - Sequential hormone therapy
    - Fulvestrant 500 mg, with a loading schedule
4. Endocrine therapy in combination with mammalian target of rapamycin (mTOR) inhibitors (everolimus) or cyclin-dependent kinase (CDK) 4/6 inhibitors (palbociclib)
5. Addition of human epidermal growth factor receptor 2 (HER2)-targeted therapy to first-line AIs
6. Use of additional biomarkers for treatment selection (in clinical trials only)

Note: The following were considered but not recommended:

- Combined endocrine therapy and chemotherapy
- Genomic or expression profiling to select treatment for hormone receptor (HR)-positive metastatic breast cancer (MBC)

Major Outcomes Considered

- Overall survival
- Progression free survival
- Time to progression
- Clinical benefit rate (stable disease plus response rate)
- Time to initiation of chemotherapy
- Toxicity
- Quality-of-life (as measured by a validated, reliable instrument [e.g., Short Form Health Survey 36])

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Systematic Literature Review

American Society of Clinical Oncology (ASCO) guidelines are based on systematic reviews. A protocol for each guideline defines the parameters for a targeted literature search, including relevant study designs, literature sources, types of reports, and prespecified study selection criteria for literature identified.

Literature Search Strategy

The MEDLINE (OVID: 2008 through week 4 of April 2014) and Cochrane Library databases (http://www.cochranelibrary.com ; to Issue 3 of March 2013) were searched for evidence reporting on outcomes of interest. Additionally, the San Antonio Breast Cancer Symposium (2011 to 2014) and ASCO abstracts (2012 to 2014) were searched for reports on systematic reviews (with or without meta-analyses) and randomized controlled trials (phase II or III) using the keywords "advanced" and "metastatic" and were reviewed for terms relating to hormone receptor (HR) status, publication type, and study design. Reference lists from seminal papers and recent review articles were scanned for additional citations, and known updates of included evidence were obtained as available. A targeted literature search update was performed in June 2015 to obtain the most recent evidence. The literature search strategy used in the MEDLINE database is available in Data Supplement 1 (see the "Availability of Companion Documents" field).

Study Selection Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were fully published or abstract reports of systematic reviews (with or without meta-analyses) or randomized controlled trials (phase II or III), published in English, that reported on any of the following interventions: endocrine therapies, including selective estrogen receptor (ER) modulators (tamoxifen or toremifene), ER downregulators (fulvestrant), progestins (megestrol acetate or medroxyprogesterone), luteinizing hormone–releasing hormone analogs (goserelin, leuprorelin, or buserelin), nonsteroidal third-generation aromatase inhibitors (AIs) (anastrozole or letrozole), and steroidal third-generation AIs (exemestane); mammalian target of rapamycin (mTOR) inhibitors (everolimus or temsirolimus); cyclin-dependent kinase (CDK) 4/6 inhibitors (palbociclib); estrogens; and chemotherapy.

Selected articles made any of the following comparisons: single-agent versus single-agent hormone

therapies, single-agent versus combination endocrine therapies, endocrine therapy with or without human epidermal growth factor receptor 2 (HER2)-targeted therapies, endocrine therapy with or without mTOR inhibitors, endocrine therapy with or without CDK 4/6 inhibitors, and endocrine therapy with or without novel agents. Articles were also required to report on primary outcomes of interest (including overall survival [OS], progression free survival [PFS] or time to progression [TTP], or clinical benefit rate [CBR; stable disease plus response rate]) or secondary outcomes of interest (including time to initiation of chemotherapy, toxicity, or quality of life [QoL] as measured by a validated, reliable instrument [e.g., Short Form Health Survey 36]). Articles were excluded from the systematic review if they were noncomparative studies.

Number of Source Documents

A total of 36 articles, including seven systematic reviews with meta-analyses (see Table 1 in the original guideline document) and 29 individual trial reports, met the inclusion criteria.

A Quality of Reporting of Meta-analyses (QUOROM) Diagram that reports the results of the literature search is available in Data Supplement 3 (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Guide for Rating Strength of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits versus harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Guide for Rating of Potential for Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low risk	No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the

Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials	
Rating of Potential for Bias	
High risk	conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction

Literature search results were reviewed and deemed appropriate for full-text review by an American Society of Clinical Oncology (ASCO) staff member in consultation with the panel co-chairs. Data were extracted by one ASCO staff member and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the co-chairs if necessary.

Study Quality

As seen in the Study Quality Assessment Table in the online Methodology Supplement (see the "Availability of Companion Documents" field), study quality was formally assessed for the 29 trials identified. Design aspects related to individual study quality were assessed by one reviewer and independently audited by another, with factors such as blinding, allocation concealment (blinding to treatment arm), placebo control, intention to treat, funding sources, and so on considered. The overall risk of bias was assessed as either low to intermediate or intermediate for the included trials. Refer to the "Rating Scheme for the Strength of the Evidence" for definitions of ratings for overall potential risk of bias.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Panel Composition

To address the clinical question, an Expert Panel was convened with multidisciplinary representation in medical oncology, radiation oncology, psycho-oncology, patient advocacy, and guideline methodology. The Expert Panel was led by two co-chairs who had the primary responsibility for the development and timely completion of the guideline.

Guideline Development Process

The Expert Panel members, who met face to face and via teleconference and corresponded through e-mail, were asked to contribute to the development of the guideline, provide critical review, interpret evidence, and finalize the guideline recommendations based on consideration of the evidence. Members of the Expert Panel were responsible for drafting the penultimate version of the guideline.

Development of Recommendations

The guideline recommendations were crafted, in part, using the GuideLines Into DEcision Support (GLIDES) methodology and accompanying BRIDGE-Wiz™ software. This method helps guideline panels systematically develop clear, translatable, and implementable recommendations using natural language, based on the evidence and assessment of its quality, to increase usability for end users. The process incorporates distilling the actions involved, identifying who will carry them out, to whom, under what circumstances, and clarifying if and how end users can carry out the actions consistently. This process helps the Panel focus the discussion, avoid using unnecessary and/or ambiguous language, and clearly state its intentions.

Rating Scheme for the Strength of the Recommendations

Guide for Types of Recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement (see the "Availability of Companion Documents" field).
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Cost Analysis

Cost Implications

The guideline panel understands that the treatment of metastatic cancer is complicated by the cost of treatment and that this may limit options in some situations. The use of combination hormone therapy, particularly with targeted agents, clearly adds both the cost of acquiring the agents as well as the cost of managing adverse effects. This guideline outlines the optimal treatment approach without considering cost or availability in specific geographic areas of the world. Recommendations are on the basis of clinical trials, and limitations of existing data are outlined. This information should help with decision making when the cost of therapy limits access to specific treatments.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Members of the Expert Panel were responsible for drafting the penultimate version of the guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and publication. All American Society of Clinical Oncology (ASCO) guidelines are reviewed and approved by the ASCO Clinical Practice Guideline Committee before publication.

The Clinical Practice Guideline Committee approved this guideline on February 16, 2016.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of endocrine therapy for hormone receptor (HR)-positive metastatic breast cancer (MBC) based on menopausal status, prior adjuvant endocrine therapy, disease-free interval, prior treatment of advanced disease, and the adverse effect profile of the treatment plan

Refer to the "Literature review and analysis" and "Clinical interpretation" sections of the original guideline document for a discussion of the potential benefits and harms of each recommendation.

Potential Harms

Data on several key adverse events are listed in Table 5 of the original guideline document. Distinctive adverse effects of hormone therapy combined with targeted agents are noted there. Clinicians and

patients should consider toxicity profiles when deciding on therapeutic options.

Refer to the "Literature review and analysis" and "Clinical interpretation" sections of the original guideline document for a discussion of the potential benefits and harms of each recommendation.

Contraindications

Contraindications

Aromatase inhibitors (AIs) are contraindicated in premenopausal women, because the reduction in tissue estrogen can lead to increased secretion of gonadotropins, causing compensatory rises in ovarian estrogens and possible induction of ovulation. This issue is most relevant for women who were premenopausal at the time of diagnosis and are now amenorrheic as a result of chemotherapy.

Qualifying Statements

Qualifying Statements

- The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied on as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.
- Refer to the original guideline document for qualifying statements related to each recommendation. Also refer to the "Health Disparities," "MCCs" and "Limitation of the Research and Future Directions" sections in the original guideline document for additional qualifying information.

Implementation of the Guideline

Description of Implementation Strategy

Guideline Implementation

American Society of Clinical Oncology (ASCO) guidelines are developed for implementation across health

settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and cancer survivors and also to provide adequate services in the face of limited resources. The guideline Bottom Line was designed to facilitate implementation of recommendations. This guideline will be distributed widely throughout the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology and Journal of Oncology Practice*. Treatments that control symptoms, delay the onset of chemotherapy, and delay progression of disease should be emphasized within the contexts of cost and toxicity.

For additional information on the ASCO implementation strategy, please see the ASCO Web site.

Implementation Tools

Clinical Algorithm

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, Fallowfield L, Fowble B, Ingle JN, Jahanzeb M, Johnston SRD, Korde LA, Khatcheressian JL, Mehta RS, Muss HB, Burstein HJ. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology guideline. J Clin Oncol. 2016 Sep 1;34(25):3069-103. [94 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Sep 1

Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

Source(s) of Funding

American Society of Clinical Oncology

Guideline Committee

Endocrine Therapy for Hormone Receptor–Positive Metastatic Breast Cancer Expert Panel

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The Expert Panel was assembled in accordance with the American Society of Clinical Oncology's (ASCO's) Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at www.asco.org/rwc). All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speakers bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the panel did not disclose any relationships constituting a conflict under the Policy.

Authors' Disclosures of Potential Conflicts of Interest

The following represents disclosure information provided by authors of the guideline. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst =

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Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Journal of Clinical Oncology Web site .

Availability of Companion Documents

The following are available:

- Clinical Practice Guideline 1-18: Endocrine therapy for hormone receptor positive metastatic breast cancer: American Society of Clinical Oncology Guideline. Methodology supplement. Alexandria (VA): American Society of Clinical Oncology; 2016. 13 p. Available from the Journal of Clinical Oncology Web site .
- Clinical Practice Guideline 1-18: Endocrine therapy for hormone receptor positive metastatic breast cancer: American Society of Clinical Oncology Guideline. Data Supplements 1-8. Alexandria (VA): American Society of Clinical Oncology; 2016. 20 p. Available from the Journal of Clinical Oncology Web site .
- Endocrine therapy for hormone receptor positive metastatic breast cancer: American Society of Clinical Oncology guideline. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2016. Available in PDF and PowerPoint from the American Society of Clinical Oncology (ASCO) Web site.
- Endocrine therapy for hormone receptor positive metastatic breast cancer: American Society of Clinical Oncology guideline. Summary of recommendations table. Alexandria (VA): American Society of Clinical Oncology; 2016. 5 p. Available from the ASCO Web site .
- Rugo HS, Rumble RB, Burstein HJ. Endocrine therapy for hormone receptor positive metastatic breast cancer: American Society of Clinical Oncology guideline summary. J Oncol Pract. 2016 Jun;12(6):583-7. Available from the Journal of Oncology Practice .

Patient Resources

The following is available:

- Hormonal therapy for metastatic breast cancer. ASCO care and treatment recommendations for

patients. [internet]. Alexandria (VA): American Society of Clinical Oncology; 2016 May 23. Available from the Cancer.Net Web site .

NGC Status

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